Food and Drug Administration
Department of Health and Human Services

FY 2004 PERFORMANCE REPORT TO THE CONGRESS

for the

Office of Combination Products

as amended in the

Medical Device User Fee and Modernization Act

Commissioner's Report

I am pleased to submit the Food and Drug Administration's fiscal year (FY) 2004 Annual Report to Congress for the Office of Combination Products (OCP). This report includes the first full year of data since OCP was established as mandated by the Medical Device User Fee and Modernization Act (MDUFMA), enacted by Congress on October 26, 2002.

Combination products are therapeutic and diagnostic products that combine elements of drugs, devices, and/or biological products. There has been much progress since oversight of their regulation was assigned to OCP. OCP has been working hard to make this often complex and relatively new regulatory area more transparent, more efficient, and better understood by both Agency reviewers and industry.

One significant regulatory issue recently addressed is the lack of a statutory definition of what constitutes the "primary mode of action" of a combination product. OCP discussed this issue in depth in a proposed rule published in May 2004. The proposed rule defines the "primary mode of action" as the single mode of action that provides the product's most important therapeutic action. Moreover, the proposed rule goes on to discuss the still more difficult problem presented by products whose most important therapeutic action cannot be determined with reasonable certainty. This is a proposal that should go a long way toward ensuring that each combination product receives the most appropriate, knowledgeable, and efficient regulatory handling. The rule provides the consistency, predictability, and transparency of the assignment process that product developers have been requesting.

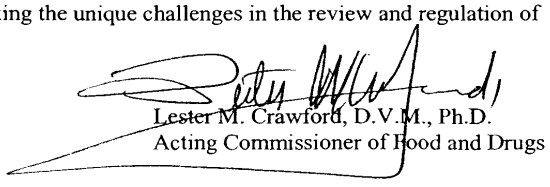
OCP also chaired working groups charged with resolving other issues of concern to both the Agency and combination product sponsors. These efforts have resulted in the publication of three draft guidance documents in FY 2004 for stakeholder review and comment that provide:

1) industry with information on submitting and resolving disputes regarding the timeliness of the premarket review of combination products;

2) a mechanism to reduce application fees for certain innovative combination products; and

3) industry with recommendations on current good manufacturing practices for combination products.

OCP has also been actively engaged in closely monitoring the timeliness of the consultation processes between Centers and offering advice and support to both industry and review staff on complex combination product issues. Their efforts this year may be best summed up by this stakeholder comment I received indicating that OCP is "extremely proactive in working with the industry to help identify and address the issues associated with regulatory challenges facing combination products.... and have done a fantastic job of listening to stakeholders, following up on their concerns, and looking for appropriate solutions for often-complex problems." We look forward to continued success in meeting the unique challenges in the review and regulation of combination products.



Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs

FY 2004 OCP Performance Report

Executive Summary

The Food and Drug Administration (FDA) established OCP on December 24, 2002, in response to MDUFMA. The mission of this office is to ensure the prompt assignment of combination products (drug-device, biologic-device, drug-biologic, or drug-device-biologic products) to Agency Centers, the timely and effective premarket review of such combination products, and consistent and appropriate postmarket regulation of these products.

This document presents OCP's annual report to Congress. OCP activities and impacts for FY 2004 highlighted in this report include the following:

- **Prompt Assignment of Combination Products**. OCP implemented a variety of measures to optimize the assignment process, and published for public review and comment a proposed rule defining "primary mode of action," the statutory criterion FDA must use when assigning a combination product to a Center for review and regulatory oversight. One hundred percent of the OCP assignments issued in FY 2004 met the 60-day decision time requirement.

- **Timely and Effective Premarket Review**. OCP provided support to sponsors and Agency Centers on a variety of products presenting complex regulatory issues to facilitate the timely and effective premarket review of combination products. OCP also actively monitored the consultation process on combination products under review to ensure that the requesting Center receives timely and constructive feedback, and has facilitated the development of processes outlining consult review responsibilities and issues to be addressed for specific product areas. OCP published a draft guidance document providing information on user fees for combination product applications in an effort to reduce the application fee burden for certain innovative combination products. OCP also published draft guidance to provide sponsors with information on submitting and resolving disputes regarding the timeliness of the premarket review of combination products. In addition, concepts and guiding principles for the number of marketing applications for combination products were formulated by a working group and are being developed into draft guidance for stakeholder comment. FDA Centers preliminarily categorized 251 original applications as combination products. All (100%) of the 78 combination product marketing applications reviewed and acted on in FY 2004 were within the review targets. Recent examples of approved combination products can be found at http://www.fda.gov/oc/combination/approvals.html.

- **Consistent and Appropriate Postmarket Regulation**. OCP published a draft guidance document on current good manufacturing practices for combination products. A working group has developed concepts and guiding principles for adverse event reporting for combination products and is working on the implementation of its recommendations. Support to sponsors and Agency Centers focused on the clarification of manufacturing and adverse event reporting regulations and coordination of headquarters and field activities for selected combination products.

In addition, OCP has implemented several educational and outreach efforts targeting stakeholders and FDA staff. Through all of its activities this year, OCP strived to ensure the prompt assignment of combination products to Agency Centers, the timely and effective premarket review of such products, and the consistent and appropriate postmarket regulation of these products to ensure the timely delivery of safe and effective combination products to the American public.

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Introduction

On October 26, 2002, Congress enacted MDUFMA. By amending the Federal Food, Drug, and Cosmetic Act, MDUFMA provided FDA with new responsibilities, resources, and challenges. Among other things, MDUFMA required FDA, not later than 60 days after the date of enactment, to establish an office within the Office of the Commissioner "to ensure the prompt assignment of combination products to agency centers, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of" combination products. As required by MDUFMA, FDA established OCP within the Office of the Commissioner on December 24, 2002. Information about OCP, including the authorizing text of the MDUFMA amendments, can be found at http://www.fda.gov/oc/combination.

MDUFMA also requires FDA to submit an annual report to Congress on the activities and impact of OCP. This document fulfills this requirement for FY 2004.

Overview of Combination Products

Combination products are increasingly incorporating cutting edge, novel technologies that hold great promise for advancing patient care. These products are defined by any of the following criteria as defined in 21 CFR § 3.2(e):

(1) Products comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose;

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Recent literature indicates that an exponential growth in the combination products market is likely over the next several years. With products such as drug-eluting stents, a spinal-fusion device incorporating a protein that promotes bone growth, a combination insulin pump and glucose monitor, and an inhalation device with live vaccine already on the market, analysts see combination products as having an increasing role in treating cancer, diabetes, hepatitis, osteoporosis, multiple sclerosis, infertility, anemia, and growth deficiencies. According to published information, products on the horizon include an artificial pancreas for treating diabetes, implantable drug pumps for treating Parkinson's disease, and catheters to inject cells to treat a damaged heart. With scientific breakthroughs, such as the Human Genome Project, drug and biological delivery technologies are advancing rapidly to find new and less invasive ways to bring improved therapeutics to patients, while at the same time improving upon safety and efficacy. Innovative drug-delivery systems, such as pulmonary, transdermal, and nasal delivery, will also pave the path for new drugs that cannot be delivered through traditional means.

Stakeholder Concerns: Combination Product Regulation

Because combination products involve components that would normally be regulated under different regulatory authorities, and frequently by different FDA Centers, they have historically raised challenging regulatory, policy, and review management issues. Prior to MDUFMA, a number of criticisms had been raised regarding FDA's regulation of combination products. These include concerns about the consistency, predictability, and transparency of the process used to assign an FDA Center with primary responsibility for review and regulation of a combination product; issues related to the management of the review process when two (or more) FDA Centers have review responsibilities for a combination product; lack of clarity about the postmarket regulatory controls applicable to combination products; and lack of clarity regarding certain Agency policies, such as when applications to more than one Center are needed.

Mandated Functions of the Office of Combination Products

FDA established OCP within the Office of the Commissioner's Office of International Activities and Strategic Initiatives on December 24, 2002. MDUFMA established broad responsibilities for OCP that cover the regulatory life cycle of drug-device, drug-biologic, and device-biologic combination products, and include product jurisdiction decisions and specific premarket review and postmarket processes. However, the primary responsibilities for scientific review and regulation of specific combination products remain in one of three product Centers – the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH) – to which they are assigned by OCP.

Specifically, the statute (503(g)(4)(B-F)) requires OCP to:

1. Promptly assign an Agency Center with primary jurisdiction for a combination product.

2. Ensure the timely and effective premarket review of combination products, by overseeing the timeliness of and coordinating reviews involving more than one Agency Center.

3. Ensure the consistency and appropriateness of postmarket regulation of combination products.

4. Resolve disputes regarding the timeliness of premarket review of combination products.

5. Review and update agreements, guidance documents or practices specific to the assignment of combination products.

OCP also serves as a focal point for addressing combination product issues raised by Agency reviewers and industry, and works with the Centers to develop guidance and/or regulations to clarify the regulation of combination products.

In addition, the Office of the Commissioner consolidated the product jurisdiction program in June 2003, giving OCP responsibility for Agency action on all Requests for Designation (RFD) submitted by industry in accordance with 21 CFR Part 3. This includes requests for classification of a particular product as a biological product, device, or drug, as well as requests for assignments of combination products.

OCP Organizational Structure

As of September 30, 2004, OCP is staffed by seven permanent positions. In addition to a Director, these positions include an Associate Director/Medical Officer, a Product Assignment Officer, a Product Classification Officer, a Senior Scientific Advisor, a Program Analyst, and a Program Support Specialist. Several additional staff members served on a rotating detail to OCP during FY 2004. Work plans provide for an eventual projected staffing size of ten positions provided financial resources to support such needed expansion are forthcoming. The office is located at: 15800 Crabbs Branch Way, Suite 200, HFG-3, Rockville, MD 20855, (301) 427-1934, fax (301) 427-1935, email: combination@fda.gov.

Report on FY 2004 OCP Activities and Impacts

This document reports the activities and impacts of OCP in the assignment of combination products and in coordinating the review and regulation of combination products for FY 2004. This document also provides a performance assessment on combination product applications acted on in FY 2004. Consistent with the mandated functions of OCP, data highlighted in the following section include:

- Prompt Assignment of Combination Products
- Timely and Effective Premarket Review
- Consistent and Appropriate Postmarket Regulation
- Effective Resolution of Review Disputes

Unless otherwise noted, all performance data in this section are as of September 30, 2004.

Activities and Impacts for FY 2004

Prompt Assignment of Combination Products

MDUFMA requires OCP to promptly assign to a Center primary jurisdiction for a combination product and to review and update agreements, guidance documents, or practices specific to the assignment of combination products. OCP is required to assign premarket review responsibility for combination products based on the product's primary mode of action (PMOA).[1] Existing intercenter agreements provide guidance on some combination product assignments. By submitting a Request for Designation (RFD), a company may obtain a formal Agency determination of a combination product's primary mode of action and of assignment of the lead Center for the product's premarket review and regulation. The Agency will make its jurisdictional determination within 60 days of filing the RFD or the sponsor's recommendation of the Center with primary jurisdiction will become the assigned center.[2] Companies and FDA Centers may also informally request assistance from OCP in working out difficult jurisdictional issues not raised in an RFD submission.

OCP FY 2004 activities and impacts related to the assignment of combination products are as follows:

- **All (100%) of the assignments due as of September 30, 2004, were issued within the 60 days provided by 21 CFR § 3.8.** RFD performance data for the assignment of combination products in FY 2004 can be found beginning on page 17 of this report.
- **Published a proposed rule describing how FDA proposes to assign a lead Center with responsibility for premarket review and regulation of a combination product.** The purpose of the proposed rule, published in the May 7, 2004, *Federal Register* (http://www.fda.gov/OHRMS/DOCKETS/98fr/oc03366.pdf) is to codify the definition of "primary mode of action." Primary mode of action is the statutory criterion to be used in assigning an Agency component to have lead premarket review responsibility for a combination product. The proposed rule clarifies and codifies principles generally used since section 503(g) of the act was enacted in 1990 and defines "primary mode of action" as the single mode of action of a combination product that provides the most important therapeutic action of the combination product. In addition, the proposed rule provides an algorithm for determining which Center would be assigned lead responsibility for the premarket review and regulation of a combination product when the most important therapeutic action of a combination product cannot be determined. The algorithm uses safety and effectiveness issues as well as consistency

[1] This is in accordance with section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(g)(1).

[2] The RFD process is outlined in 21 CFR Part 3. Information required in an RFD submission is outlined in 21 CFR § 3.7.

with the regulation of similar products to guide the assignment of combination products in such cases. Issuance of this proposal furthers MDUFMA's requirement that OCP review practices specific to the assignment of combination products, consult with stakeholders and Center directors, and make a determination whether to modify those practices. The initial 60-day comment period was extended to August 20, 2004. Comments are being analyzed and publication of a final rule is expected in 2005.

- **Published capsular descriptions of selected jurisdictional decisions on OCP's Internet page.** These descriptions of approximately 70 prior FDA RFD decisions are general in nature in order to protect trade secret and confidential commercial information and are intended to improve the transparency of the jurisdiction process. The descriptions are grouped by Center and cover both combination and non-combination products. OCP will continue to evaluate the extent to which RFD decisions can be suitably described based upon publicly available information and other relevant factors in order to expand this list in the future. The list is available at http://www.fda.gov/oc/combination/determinations.html.

- **Published a document on OCP's Internet site clarifying the jurisdiction of biological products as a result of the transfer of some therapeutic biological products to CDER.** This document, available at http://www.fda.gov/oc/combination/transfer.html, is intended to help industry understand the jurisdiction of therapeutic biological products in FDA. It identifies the categories of therapeutic biological products transferred from CBER to CDER and the categories of therapeutic biological products for which CBER retains regulatory responsibility. A related document (http://www.fda.gov/cder/biologics/default.htm) clarifies how jurisdiction questions for combinations of drug-biologic products reviewed entirely within CDER can be determined.

- **Published a jurisdictional update concerning Human Demineralized Bone Matrix on OCP's Internet page.** This document, available at http://www.fda.gov/oc/combination/bone.html, provides clarification on the regulation of human demineralized bone matrix (DBM). Human DBM, when used alone, is regulated solely under section 361 of the Public Health Service Act. However, when combined with certain other components to assist in the filling of bone voids, such DBM products are regulated under the medical device provisions of the Federal Food, Drug, and Cosmetic Act. This document was published in an effort to keep stakeholders apprised of significant jurisdictional decisions.

- **Continued to streamline the internal process and timeline for the prompt and efficient review of RFDs**. Established internal criteria for determining when Office of General Counsel (OGC) review and clearance of an RFD assignment letter is required. It is anticipated that this new process will improve coordination with OGC and shorten the timeframes for rendering decisions on formal RFDs for certain products.

- **Developed templates for RFD decision letters.** These templates expedite the preparation of, and ensure the consistency of information contained in, RFD decision letters.

- **Developed an internal database of RFD determinations to facilitate the timely consideration of new assignment requests**. In addition, OCP collaborated with CDRH to integrate RFD tracking and documentation with CDRH's new Division Tracking System. The integration of these two systems will enhance CDRH's efficiency in consulting on RFD requests, and OCP is exploring the feasibility of making this system available to CDER and CBER.
- **Conducted monthly product jurisdiction meetings for the exchange of information between OCP jurisdictional and assignment specialists, and CBER, CDER, and CDRH product jurisdiction officers.** This venue provides for an open discussion of, and progress report on, RFD's and other jurisdictional decisions pending or made in the Centers, and enhances the consistency and clarity of jurisdictional decisions across the Agency.
- **Responded to external and internal stakeholder inquiries by providing advice, guidance, and clarification on a variety of informal requests related to the assignment of combination products.** OCP responded to over 175 stakeholder inquiries on issues ranging from the assignment process itself to jurisdictional issues on a wide range of specific combination products in areas including orthopedic, neurology, pulmonology, allergy, anesthesia, cardiology, dermatology, dentistry, otolaryngology, obstetrics and gynecology, urology, radiology, photodynamic therapy, in vitro diagnostics, tissue engineering, gene therapy, vaccine, orphan products, iontophoresis, antimicrobials (including antivirals), wound healing products, pain relief products, absorbable hemostatic agents, and novel drug delivery systems.

Timely and Effective Premarket Review

MDUFMA requires OCP to ensure the timely and effective premarket review of combination products by overseeing the timeliness of reviews and coordinating reviews involving more than one Agency Center. On July 31, 2002, FDA issued an internal document to provide the policies and procedures for FDA staff to follow when requesting, receiving, handling, processing, and tracking formal consultative and collaborative reviews of combination products, devices, drugs, and biologics. The objectives are to improve intercenter communication on combination products, as well as the timeliness and administrative consistency in the conduct of intercenter consultative and collaborative reviews. This document is available at http://www.fda.gov/oc/combination/consultative.html.

Premarket Review

OCP FY 2004 activities and impacts related to premarket review are as follows:

- **Facilitated the premarket review processes for a variety of combination products presenting complex regulatory issues**. Responding to requests from both industry and Agency review staff, OCP facilitated meetings and discussions at key milestones in the review process to ensure continued and consistent communication by the review staff, including clearly delineated regulatory paths for marketing authorization

review. The practices and processes developed as a result of these actions serve as models for the review of submissions of similar products.

- **Facilitated communication between Centers and sponsors**. OCP facilitated meetings and communications on a number of specific issues/products that contribute to ensuring the timely and effective review of combination products. Examples included: handling of changes to product design, product specifications, test methods or indications for use; Centers for Medicare and Medicaid Services (CMS) reimbursement for device components of investigational combination products, user fees, pharmacogenomics, nanotechnology, novel drug delivery technology, tissue engineering, hyperthermia, cryosurgery, over-the-counter drugs, pre-filled syringes, cross-labeling, drug eluting stents, orphan products, software, and Master Files. The combination product areas included: pediatrics, urology, orthopedics, oncology, pulmonology, anesthesiology, ophthalmology, cardiology, endocrinology, neurology, in vitro diagnostics, antimicrobial therapy, gynecology, radiology, photodynamic therapy, tissue products, ultrasonography, iontophoresis, vaccines, transdermal patch technology, infusion pumps, and wound-healing products.

- **Published a draft guidance document entitled "Guidance for Industry and FDA Staff: Application User Fees for Combination Products."** The document went on display on September 23, 2004. The guidance provides information on marketing application user fees for combination products. In particular, the document describes how the PDUFA "barrier to innovation" waiver provision may be applied to innovative products in the infrequent situation where FDA requires two marketing applications. This waiver would provide a reduction in application user fees equivalent to the additional fee burden associated with the submission of two applications. Comments are due November 29, 2004. The draft guidance document is the result of a collaborative working group effort chaired by OCP and consisting of experts from CBER, CDER, CDRH, and OGC. This document is available at http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0410-gdl0001.pdf.

- **Chaired a working group to consider the number, format, and content of marketing applications for combination products**. This group is comprised of experts from CBER, CDER, CDRH, and OGC. The team developed guiding principles for determining whether one or two marketing applications is appropriate for a combination product. A draft guidance document for industry and FDA staff providing factors to consider in determining the appropriate number of marketing applications for a combination product is under internal review in the Agency. Publication is expected in early 2005. Members of the working group also engaged in discussions with the Agency's expert on electronic submissions and the Common Technical Document (CTD), concerning the format and content of applications for combination products. Recommendations for the format and content of combination product applications will be made in conjunction with the Agency's work with the CTD and electronic-CTD formats.

- **Chaired a working group to consider principles concerning the requirement for mutually conforming labeling for combination products.** This team consists of experts from CBER, CDER, CDRH, and OGC. The Agency plans to hold a public

meeting in FY 2005 to obtain stakeholder input on this complex and challenging issue.

- **Participated in various intercenter working groups clarifying issues related to combination products.** The working groups are developing policies and guidances for the development, jurisdiction and assignment, and/or regulatory review of new technologies and classes of combination products. Topics covered by specific working groups include prevention and treatment of device related infections, drug eluting stents, nanotechnology, oncology, tissues, and pharmacogenomics.
- **Responded to inquiries from FDA staff on the appropriate use and interpretation of the combination products algorithm and associated categories**. The categories for combination products are based on the types of regulatory issues the products present, for example, a prefilled drug or biologic delivery system, a device combined with a drug or biologic, a co-packaged product or kit, or separate products with mutually conforming labeling. All premarket applications in CBER, CDER, and CDRH are categorized as to whether or not they concern a combination product, and if so, what type.
- **Analyzed monthly reports from CBER, CDER, and CDRH capturing data on the categorization of combination products.** Data on new product applications in CBER and CDER and approved product applications in CDRH are reviewed to ensure that combination product categories are being accurately assigned. Errors are reported to the Centers for correction to ensure the accuracy of the data reported annually to Congress on the numbers and types of combination products under review, as required by MDUFMA. These data are also used by OCP to monitor the progress of premarket applications for combination products under review by the Agency.

Consultative/Collaborative Review Process

OCP FY 2004 activities and impacts related to the consultative/collaborative review process are as follows:

- **Developed an intercenter training program for CBER, CDER, and CDRH reviewers engaged in the intercenter consult review process of premarket submissions.** The purpose of the training is to provide reviewers in each medical product Center with an understanding and insight into the premarket review, regulatory processes, policies, and procedures in their sister Centers in order to facilitate timely interaction, communication, and responsiveness on intercenter consultative and collaborative reviews of premarket submissions. The first training session, "Introduction to CDER for CBER and CDRH Reviewers," was held on October 5, 2004. Planning for subsequent sessions is in progress.
- **Provided support to review staff to facilitate the intercenter consultation process**. Examples include identification of consulting divisions and contacts, clarification of due dates and completion status, facilitating access to electronic review documents, ensuring effective performance of courier service specifically established for delivery of intercenter consult requests, clarification of the specific review requirements, and identification and resolution of barriers to timely completion of consultation requests.

- **Facilitated intercenter communication and procedures to delineate the consult review process and issues to be considered for specific product areas.** These include hyperthermia devices used in combination with drug or biologic agents for the treatment of cancer, and cardiovascular devices incorporating drug products. Established a shared drive and an eRoom to facilitate the sharing and real-time review of applications. These mechanisms provide for enhanced communication across Centers utilizing different databases and tracking systems that cannot readily be linked.
- **Actively monitored the intercenter consultation process on combination products under review to ensure that the requesting Center received timely and constructive feedback**. OCP tracked a total of 210 intercenter consult requests in FY 2004 (see table on page 22).
- **Completed development of and began testing an internal, web-enabled database that will provide for electronic completion, monitoring, and tracking of all consultation requests occurring between CBER, CDER, and CDRH**. A pilot of the application is slated for early FY 2005.

Consistent and Appropriate Postmarket Regulation

MDUFMA requires OCP to ensure the consistency and appropriateness of postmarket regulation of combination products. OCP FY 2004 activities and impacts related to the consistency of postmarketing regulation are as follows:

- **Published a draft guidance document entitled "Guidance for Industry and FDA, Current Good Manufacturing Practice for Combination Products."** The document went on display September 29, 2004. This draft document was published in conjunction with the release of the Agency's Final Report "Pharmaceutical cGMPs for the 21t Century – A Risk-Based Approach." The draft guidance makes recommendations for achieving compliance with applicable current good manufacturing practices requirements for the drug, device, or biological product constituent parts of a combination product, or where such components are separately marketed. In addition, the draft guidance document makes recommendations for achieving compliance with applicable current good manufacturing practices requirements for combination products that are co-packaged or produced as a single entity. The guidance is responsive to stakeholder concerns that it should generally not be necessary for manufacturers to maintain two separate manufacturing systems (e.g. 21 CFR Part 210 and 211 for drugs/biological products and 21 CFR Part 820 for devices) for a combination product. The draft guidance document is the result of a working group collaboration chaired by OCP and consisting of experts from CBER, CDER, CDRH, and OGC. The document is available at http://www.fda.gov/oc/combination/OCLove1dft.pdf.
- **Chaired a working group to develop policy and guidance on the application of adverse event reporting regulations for combination products**. The group developed guiding principles on the factors to be considered when determining the appropriate requirements for safety reporting for combination products and procedures that FDA recommends for reporting postmarket mandatory adverse events for

combination products. The group is currently considering how best to implement its recommendations.

- **Participated in an Agency working group developing recommendations for changes to the 3500 and 3500A MedWatch forms for reporting adverse events.** Recommended changes to the forms that will help to identify adverse events associated with combination products in order to facilitate appropriate intercenter communication, review, and analysis of suspected adverse reactions.
- **Provided support to Centers and sponsors to ensure the consistency and appropriateness of postmarket regulation of combination products.** Examples include clarifying the application of current good manufacturing practices (cGMP) and quality systems (QS) regulations for compliance inspections of combination products; clarifying appropriate mechanisms and manufacturer responsibilities for reporting adverse events for combination products; outlining import requirements for combination products; and facilitating the intercenter discussion of reporting approaches for certain classes of products.

Effective Resolution of Review Disputes

MDUFMA requires OCP to resolve disputes regarding the timeliness of the premarket review of a combination product. OCP FY 2004 activities and impacts related to the effective resolution of review disputes are as follows:

- **Published a draft guidance document entitled "Combination Products, Timeliness of Premarket Reviews, Dispute Resolution Guidance."** This document, published in the *Federal Register* on May 4, 2004, describes a premarket timeliness dispute as arising when FDA does not review and act on an applicant's submission within the applicable performance goal set by the Prescription Drug User Fee Act (PDUFA) or MDUFMA. The draft guidance includes the timelines and process for presenting a dispute resolution to OCP, information that should be included in each timeliness dispute resolution request, and how OCP will respond to such requests. Stakeholder comments have been reviewed and publication of final guidance is expected in FY 2005. This document is available at http://www.fda.gov/oc/combination/dispute.pdf.

Additional Activities and Impacts

Additional activities and impacts of OCP in FY 2004 are as follows:

- **Participated in the Agency's Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach initiative as a member of the GMP Harmonization Analysis working group.** Members of this group also served on the combination products cGMP/QS regulations policy group chaired by OCP. The work of these two groups dovetailed to form the basis of the recommendations in the draft guidance document on cGMPs for combination products.

- **Advanced the Agency's initiative for Improving Innovation in Medical Technology:**
    - **Participated in the FDA intercenter working group on Innovative Systems for Delivery of Drugs and Biologics.** The working group published a summary of the FDA public workshop "Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical and Regulatory Challenges," held in July 2003. The summary is published at http://www.fda.gov/oc/combination/workshop070803.html. The working group is drafting a guidance document addressing stakeholder comments from the workshop as well as comments from a cross-Center survey of FDA staff on combination products. The draft document will be circulated for internal comment with publication expected in FY 2005. The document, which emphasizes early and frequent communication with FDA, is intended to serve as a starting point for product developers. OCP has assumed the lead for the clearance and publication of this guidance document.
    - **Co-chaired the FDA/Drug Information Agency (DIA) Pharmacogenomics Workshop, "Co-Development of Drug, Biological, and Device Products," conducted on July 29, 2004.** This workshop was conducted to obtain stakeholder input on the identification of the important issues in the co-development of pharmacogenomic combination products as a first step in the development of guidance for industry and FDA on the co-development of pharmacogenomic combination products for therapeutic and diagnostic use.
- **Coordinated discussions concerning Centers for Medicare and Medicaid Services (CMS) reimbursement for certain combination products.** Developed options for the potential reimbursement of device components of combination products being studied under an IND.
- **Conducted 22 presentations to external stakeholders and 8 presentations to FDA staff for education, outreach, and training purposes.** Stakeholder presentations focused on the assignment and regulation of combination products and discussion of OCP activities, initiatives, proposed regulations, and guidances. Internal presentations were focused on raising awareness of combination product issues, including the intercenter consultation process; the identification and categorization of combination product applications; and jurisdiction issues and GMP considerations for combination products. Recent OCP presentations are posted at http://www.fda.gov/oc/combination/presentations/default.htm.
- **Obtained input from Internal and External Stakeholders**.
    - Met with trade associations and coalitions representing the drug, device, and biologics industries. Discussions focused on emerging issues in combination product regulation, the role of OCP, policies and guidances under consideration, monitoring intercenter consults, PMOA, and dispute resolution.
    - Conducted quarterly meetings with CBER, CDER, CDRH, and Agency senior executive management to discuss key areas of combination products regulation and to discuss and gain support for OCP activities and initiatives.

- Met with other Agency senior executive management officials to brief them on OCP roles, responsibilities, and ongoing initiatives.

- **Responded to a variety of press inquiries about combination product regulation and OCP roles and responsibilities.** Reviewed and provided input on a variety of external articles and reports for publication on the regulation of combination products.

Report on FY 2004 OCP Requirements

This report provides preliminary performance statistics for FY 2004 and updates the FY 2003 data in Appendix A. MDUFMA requires OCP to provide a performance assessment on combination product applications acted on in FY 2004. Consistent with the mandated functions of the OCP, data highlighted in this section include:

- Timeliness in days of the assignment of combination products
- Number and types of combination products under review
- Timeliness in days of the reviews of combination products
- Number of premarket reviews of combination products that involved a consulting Agency Center

The following information refers to FDA performance presented in this report.

- OCP, CBER, CDER, and CDRH developed a process to collect the necessary data and report on the required information enacted in MDUFMA. This process was implemented April 1, 2003.
    - CBER's and CDER's data collection systems identify combination product status when applications are submitted for review. Review performance statistics are based on a fiscal year receipt cohort; this methodology calculates performance statistics for applications for the fiscal year FDA received them, regardless of when FDA ultimately acted on or approved the submissions.
    - CDRH's data collection system records this information at application close-out (when review decisions are made). Review performance statistics are based on the fiscal year when decisions are made or the close-out of the applications; this methodology calculates performance statistics for applications for the fiscal year FDA reviewed and made decisions on them, regardless of when FDA received the applications.
- Unless otherwise noted, all performance data in this section are as of September 30, 2004.

Prompt Assignment of Combination Products

Requirement – Report the timeliness in days of the assignment of combination products

FDA is required to assign premarket review responsibility for combination products based on the product's primary mode of action. By submitting an RFD, a company may obtain a formal FDA determination of a combination product's primary mode of action and of assignment of the lead Center for the product's premarket review and regulation. OCP must make its jurisdictional determination within 60 days of filing the RFD or the sponsor's recommendation of the Center with primary jurisdiction will become the assigned Center.

Requirement Type	Requirement Timeframe
Request for Designation	60 calendar days

Workload

During FY 2004, 32 requests for assignment of products determined to be combination products were received. In addition, there was one request for assignment pending at the beginning of this period. Of these 33 requests, 26 assignments have been issued (3 to CBER, 6 to CDER, and 17 to CDRH). Twenty of the products were determined to be drug-device combinations, five were device-biologic combinations, and one was a drug-device-biologic combination. Of the seven remaining requests, three were withdrawn from consideration by the sponsor and four were still pending and not overdue as of September 30, 2004.

Combination Product Assignments Issued FY 2004	
Primary Center	**Number of Product Assignments Issued**
CBER	3
CDER	6
CDRH	17
Total Assigned	26

Prompt Assignment of Combination Products

Performance

As of September 30, 2004, all 26 assignments issued were within 60 days with a median assignment time of 35 days. Total FDA combination product assignment time is equal to the number of calendar days from receipt of the RFD to the date of issuance of the letter of Center assignment by OCP to the sponsor. More detailed FY 2004 RFD performance information, including OCP's review of RFDs for non-combination products, is available at http://www.fda.gov/oc/combination/fy04rfd.html. The table below summarizes FDA's performance for these assignments issued in FY 2004.

Combination Product Requests for Assignment FY 2004

Total Requests for Assignment Submitted[3]	Product Assignments[4] Issued	Product Assignments Pending[5] (not overdue)	Product Assignments Pending (overdue)	Product Assignments (Percent) Within 60 days	Median Product Assignment Time[6] (days)	Range of Product Assignment Time (days)
33	26	4	0	26 (100%)	35	18 to 59

[3] Includes one that was pending at the beginning of the period.

[4] Does not include one request for reconsideration that was issued within the 15-day timeframe provided by 21 CFR § 3.8.

[5] Three applications were withdrawn.

[6] This represents the median assignment time of FY 2004 assignments, indicating half of the assignments were issued before this time and half of the assignments were issued after this time, that have been issued as of September 30, 2004. Updated numbers will be presented in the FY 2005 report.

Timely and Effective Premarket Review

Requirement – Report the number and types of combination products under review

During FY 2004, the Agency preliminarily categorized 251 original applications under review as combination products. Of these, CBER received and categorized as combination products 37 applications; CDER received and categorized as combination products 114 applications; and CDRH categorized 100 applications, which were reviewed and acted on as of September 30, 2004. Each combination product is classified into one of nine categories using a categorization methodology developed for this purpose. The table below reflects the number of original applications preliminarily categorized as combination products in FY 2004.

Application Type	Combination Product Category - FY 2004									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**TOTALS**
Original NDAs	3	13	--	2	--	--	1	--	--	**19**
Original BLAs	1	--	2	--	--	--	--	--	--	**3**
Original PMAs	--	1	--	3	1	--	1	1	--	**7**
510(k)s	1	1	--	50	4	--	6	2	3	**67**
Original INDs	3	42	11	5	11	5	13	25	11	**126**
Original IDEs	--	--	--	16	9	--	1	1	--	**27**
Original HDEs	--	--	--	--	2	--	--	--	--	**2**
TOTALS	**8**	**57**	**13**	**76**	**27**	**5**	**22**	**29**	**14**	**251**

APPLICATION KEY:

NDAs = New Drug Applications
BLAs = Biologics License Applications
PMAs = Premarket Approval Applications
510(k)s = Premarket Notifications
INDs = Investigational New Drug Applications
IDEs = Investigational Device Exemptions
HDEs = Humanitarian Device Exemptions

COMBINATION PRODUCT KEY:

1 = convenience kit or co-package
2 = prefilled drug delivery device/system
3 = prefilled biologic delivery device/system
4 = device coated/impregnated/otherwise combined with drug
5 = device coated or otherwise combined with biologic
6 = drug/biologic combination
7 = separate products requiring mutually conforming labeling
8 = possible combination based on mutually conforming labeling of separate products
9 = other type of combination product

Timely and Effective Premarket Review

Requirement – Report the timeliness in days of the reviews of combination products

Fiscal Year Cohorts - The FDA review performance statistics are calculated differently for the Centers:

- CBER and CDER – review performance statistics are based on a fiscal year receipt cohort; this methodology calculates performance statistics for applications for the fiscal year FDA received them, regardless of when FDA ultimately acted on or approved the submissions.
- CDRH – review performance statistics are based on the fiscal year when marketing authorization decisions are made; this methodology calculates performance statistics for applications for the fiscal year FDA made decisions on them, regardless of when FDA received the applications.

Because both approaches report on a specific FY cohort, the statistics shown for a particular year may change from one report to the next. This report provides preliminary performance statistics for FY 2004 and updates the FY 2003 data in Appendix A.

The table below summarizes the combination product application, review type, and the review target.

Application Type	Review Type	Review Within
Original NDAs	Priority	6 months
	Standard	10 months
Original BLAs	Priority	6 months
	Standard	10 months
Original PMAs	Expedited	180 days
	Original	180 days
Original 510(k)s	Special	30 days
	Abbreviated	90 days
	Traditional	90 days

CBER and CDER Combination Products

While it is too early to report final review performance statistics for marketing applications submitted in FY 2004 for CBER and CDER, the one original priority NDA has been reviewed and acted on within the 6-month review target. The four original standard NDAs have been reviewed and acted on within the 10 months with a median review time of 301 days (9.9 months). The 1 priority NDA, 13 standard NDAs, 3 standard BLAs, and 1 traditional 510(k) are pending and not overdue as of September 30, 2004.

CBER and CDER Combination Products Received FY 04

Application Type	Review Type	Review Within	Reviewed and Acted On	Number Pending and Not Overdue	Median or Actual Review Time[7] (days)	Range of Review Time[8] (days)	Number (Percent) on Time
Original NDAs	Priority	6 months	1	1	182	--	1 (100%)
	Standard	10 months	4	13	301	106 to 305	4 (100%)
Original BLAs	Priority	6 months	--	--	--	--	--
	Standard	10 months	--	3	--	--	--
Original 510(k)s	Traditional	90 days	--	1	--	--	--

[7] This represents the median review time of FY 2004 submissions, indicating half of the application review times were below this time and half were above this review time, that have been acted on as of September 30, 2004.

[8] Some product review goals (e.g., NDAs) are determined by review months. Due to the fluctuation in days of individual months (i.e., 28 to 31), 10 months can range from 303 days (e.g., February 1 to December 1) to 306 days (e.g., March 15 to January 15) and 6 months can range from 182 days (e.g., February 15 to August 15) to 184 days (e.g., July 15 to January 15).

Timely and Effective Premarket Review

CDRH Combination Products

FDA reviewed and acted on six original PMAs for combination products in FY 2004. All 6 original PMAs were reviewed and acted on within the 180-day review target with a median cycle review time of 131.5 days and median total review time of 303.0 days.[9]

FDA reviewed and acted on 67 original 510(k)s for combination products in FY 2004. All six special 510(k)s were reviewed and acted on within the 30-day review target. All 4 abbreviated 510(k)s and 57 traditional 510(k)s were reviewed and acted on within the 90-day review target.[10] The median cycle/total review times for special, abbreviated, and traditional 510(k)s were 20.5/20.5 days, 70.0/123.5 days and 71.0/96.0 days, respectively.

CDRH Combination Product PMAs and 510(k)s FY 2004

Application Type	Review Type	Review Within	Reviewed and Acted On	Median Cycle Review Time[11] (days)	Range of Cycle Review Time (days)	Median Total Review Time[12] (days)	Number (Percent) on Time
Original PMAs	Expedited	180 days	--	--	--	--	--
	Original	180 days	6	131.5	53 to 178	303.0	6 (100%)
Original 510(k)s	Special	30 days	6	20.5	11 to 30	20.5	6 (100%)
	Abbreviated	90 days	4	70.0	10 to 88	123.5	4 (100%)
	Traditional	90 days	57	71.0	3 to 90	96.0	57 (100%)

[9] Considers whether FDA review time remained within 180 days for Original and Expedited PMAs, with FDA's review clock being reset whenever additional information is received in accordance with 21 CFR 814.37.

[10] Considers whether FDA review time remained within 30 days for Special 510(k)s and 90 days for Traditional and Abbreviated 510(k)s, with FDA's review clock being reset to zero whenever additional information is received in accordance with 21 CFR 807.87(1).

[11] Median cycle review time is based on all FDA review cycles. For example, if four Abbreviated 510(k)s are reviewed and acted on within one review cycle, three abbreviated 510(k)s are reviewed and acted on within two review cycles, and two Abbreviated 510(k) are reviewed and acted on within three review cycles, the total number of review cycles for calculating the median review time is nine review cycles.

[12] Median total review time is based on the total FDA review time. For example, if one Abbreviated 510(k) is acted on after three review cycles, all three review cycles are added together to determine the total review time. Each combination product review time total is calculated, and the total review times are then sorted from low to high. The median total review time is then calculated.

Timely and Effective Premarket Review

Requirement – Report the number of premarket reviews of combination products that involved a consulting Agency Center

The Intercenter Requests for Consultative or Collaborative Review forms data received during FY 2004 are indicative of the number of premarket reviews of combination products that involved a consulting Agency Center.[13] As the primary assigned Center, CBER requested 20 Intercenter Consultations (4 consultations with CDER, 16 consultations with CDRH), CDER requested 59 Intercenter Consultations (2 consultations with CBER, 57 with CDRH), and CDRH requested 131 intercenter consultations (9 with CBER, 122 with CDER).[14] The table below reflects the Intercenter Requests for Consultative or Collaborative Review forms received and monitored by OCP during FY 2004.

		Consulting Center			Number of Consults
		CBER	CDER	CDRH	
Primary Assigned Center	CBER	---	4	16	20
	CDER	2	---	57	59
	CDRH	9	122	---	131
	Totals	11	126	73	210

[13] Some applications were associated with multiple consulting requests. Additionally, because these consulting requests are associated with any combination product under review for which consultative or collaborative review is needed, regardless of the date of FDA receipt of the application, the number of requests is not directly comparable to the number of combination product applications received during FY 2004 as reported in the previous section.

[14] The web-enabled database being developed to provide for electronic completion, monitoring, and tracking of combination products consult requests will automate this process and better ensure reporting of all such requests to OCP.

Effective Resolution of Review Disputes

Requirement – Report the timeliness in days of dispute resolutions regarding combination products

There have been no formal requests to resolve a dispute regarding the timeliness of a combination product review received during this reporting period. The "Activities and Impacts for FY 2004, Premarket Review" section of this report provides examples of informal facilitation and resolution of issues related to premarket review.

APPENDIX A: Workload and Performance 2003 Update

Prompt Assignment of Combination Products

Workload

Since the establishment of OCP on December 24, 2002, through September 30, 2003, 16 requests for assignment of products determined to be combination products were received. Ten of the products were determined to be drug-device combinations, two were device-biologic combinations, and one was a drug-biologic combination. Of these 16 requests, 13 assignments were issued (two to CBER, three to CDER, and eight to CDRH). Of the three remaining requests, two were withdrawn from consideration and the other request was still pending and not overdue as of September 30, 2003. The table below is updated to reflect the number of requests for assignment received through September 30, 2003.

Combination Product Assignments Issued FY 2003	
Primary Center	**Number of Product Assignments Issued**
CBER	2
CDER	3
CDRH	8
Total Assigned	13

Performance

As of September 30, 2003, all 13 combination product assignments were issued within 60 days with a median assignment time of 41 days. Total FDA combination product assignment time is equal to the number of calendar days from receipt of an RFD submission by a sponsor to the date of issuance of the letter in which OCP designates a lead Center assignment. The table below summarizes the assignments issued from December 24, 2002 through September 30, 2003.

Combination Product Requests for Assignment December 24, 2002 through September 30, 2003						
Total Requests for Assignment Submitted	**Product Assignments Issued[15]**	**Product Assignments Pending[16] (not overdue) as of 9/30/04**	**Product Assignments Pending (overdue)**	**Product Assignments (Percent) Within 60 days**	**Median Product Assignment Time [17] (days)**	**Range of Product Assignment Time (days)**
16	13	1	0	13 (100%)	41	18 to 48

[15] Total does not include one request for reconsideration that was responded to within the 15-day timeframe provided in 21 CFR § 3.8.

[16] Two applications were withdrawn.

[17] This represents the median assignment time of FY 2003 assignments, indicating half of the assignments were issued before this time and half of the assignments were issued after this time, that have been issued as of September 30, 2003.

Timely and Effective Premarket Review of Combination Products – Timeliness of Premarket Reviews

From April 1, 2003, through September 30, 2003, the Agency received 96 original applications for review categorized by the Centers as combination products. Of these, CBER received and categorized as combination products 25 applications; CDER received and categorized as combination products 31 applications; and CDRH categorized as combination products 40 applications, which were reviewed and acted on as of September 30, 2003. The table below reflects the number of original applications categorized as combination products through September 30, 2003.

Application Type	Combination Product Category April 1, 2003 through September 30, 2003									
	1	2	3	4	5	6	7	8	9	TOTALS
Original NDAs	--	7	--	1	--	--	--	--	--	**8**
Original BLAs	1	--	1	--	--	--	--	--	--	**2**
Original PMAs	--	--	--	1	--	--	1	--	--	**2**
510(k)s	3	1	--	10	2	--	5	--	2	**23**
Original INDs	2	15	4	--	5	3	4	6	5	**44**
Original IDEs	3	1	--	9	--	--	2	--	1	**16**
Original HDEs	--	--	--	--	1	--	--	--	--	**1**
TOTALS	**9**	**24**	**5**	**21**	**8**	**3**	**12**	**6**	**8**	**96**

APPLICATION KEY:

NDAs = New Drug Applications
BLAs = Biologics License Applications
PMAs = Premarket Approval Applications
510(k)s = Premarket Notifications
INDs = Investigational New Drug Applications
IDEs = Investigational Device Exemptions
HDEs = Humanitarian Device Exemptions

COMBINATION PRODUCT KEY:

1 = convenience kit or co-package
2 = prefilled drug delivery device/system
3 = prefilled biologic delivery device/system
4 = device coated/impregnated/otherwise combined with drug
5 = device coated or otherwise combined with biologic
6 = drug/biologic combination
7 = separate products requiring mutually conforming labeling
8 = possible combination based on mutually conforming labeling of separate products
9 = other type of combination product

CBER and CDER Combination Products

As previously noted, CBER and CDER base their calculations on the fiscal year receipt cohort for the combination products. FDA reviewed and acted on seven of the eight standard original NDAs within 10 months. The one remaining standard original NDA is pending and not overdue as of September 30, 2004. FDA reviewed and acted on two standard original BLAs within the 10-month review target. The table below reflects FDA's performance for these submissions that were received between April 1, 2003, and September 30, 2003, and reviewed and acted on through September 30, 2004.

CBER and CDER Combination Products Received April 1, 2003 to September 30, 2003

Application Type	Review Type	Review Within	Reviewed and Acted On	Number Pending and Not Overdue	Median Review Time[18] (days)	Range of Review Time[19] (days)	Number (Percent) on Time
Original NDAs	Priority	6 months	--	--	--	--	--
	Standard	10 months	7	1	303	119 to 306	7 (100%)
Original BLAs	Priority	6 months	--	--	--	--	--
	Standard	10 months	2	--	293	283 to 302	2 (100%)

[18] This represents the median review time of FY 2003 submissions, indicating half of the application review times were below this time and half were above this review time, that have been acted on as of September 30, 2004.

[19] Some product review goals (e.g., NDAs) are determined by review months. Due to the fluctuation in days of individual months (i.e., 28 to 31), 10 months can range from 303 days (e.g., February 1 to December 1) to 306 days (e.g., March 15 to January 15) and 6 months can range from 182 days (e.g., February 15 to August 15) to 184 days (e.g., July 15 to January 15).

CDRH Combination Products

FDA reviewed and acted on one expedited PMA and one original PMA within the 180-day review target as of September 30, 2003. Both PMAs were reviewed and acted on within the 180-day review target with a median cycle review time of 82 days and an actual cycle review time of 180 days, respectively.

FDA reviewed and acted on 23 original 510(k)s for combination products in FY 2003. All three special 510(k)s were reviewed and acted on within the 30-day review target. The one abbreviated 510(k) and all 19 traditional 510(k)s were reviewed and acted on within the 90-day review target. The median cycle/total review times for special, abbreviated, and traditional 510(k)s were 28/38 days, 70/140 days, and 79/90 days, respectively.

CDRH Combination Product PMAs and 510(k)s
April 1, 2003 to September 30, 2003

Application Type	Review Type	Review Within	Reviewed and Acted On	Median Cycle Review Time (days)	Range of Cycle Review Time (days)	Median Total Review Time (days)	Number (Percent) on Time
Original PMAs	Expedited	180 days	1	82	58 to 106	246	1 (100%)
	Original[20]	180 days	1	--	180	--	1 (100%)
Original 510(k)s	Special	30 days	3	28	10 to 29	38	3 (100%)
	Abbreviated	90 days	1	70	63 to 77	140	1 (100%)
	Traditional	90 days	19	79	19 to 90	90	19 (100%)

[20] No median was calculated as there was only one review cycle. Therefore, the cycle review time of 180 days was equal to the total review time.

Timely and Effective Premarket Review of Combination Products – Intercenter Consultation Requests

The Intercenter Requests for Consultative or Collaborative Review forms data received in OCP during 2003 are indicative of the number of premarket reviews of combination products that involved a consulting Agency Center.[21] As the primary assigned Center, CBER requested 25 Intercenter Consultations (8 consultations with CDER, 17 consultations with CDRH), CDER requested 21 Intercenter Consultations (3 consultations with CBER, 18 with CDRH), and CDRH requested 52 intercenter consultations (7 with CBER, 45 with CDER).[22] The table below reflects the Intercenter Requests for Consultative or Collaborative Review forms received and monitored by OCP during 2003.

		Consulting Center			Number of Consults
		CBER	CDER	CDRH	
Primary Assigned Center	CBER	---	8	17	25
	CDER	3	---	18	21
	CDRH	7	45	---	52
	Totals	10	53	35	98

[21] Some applications were associated with multiple consulting requests. Additionally, because these consulting requests are associated with any combination product under review for which consultative or collaborative review is needed, regardless of the date of FDA receipt of the application, the number of requests is not directly comparable to the number of combination product applications received since April 1, 2003, as reported in the previous section.

[22] During this initial start-up phase of this process, it is likely that not all intercenter requests for consultations were submitted to the OCP for tracking and monitoring purposes. The web-enabled database being developed to provide for electronic completion, monitoring, and tracking of combination products consult requests will automate this process and better ensure submission of all such requests to OCP. Educational efforts on the process and procedures for intercenter consult reviews will continue.

APPENDIX B: Glossary

Biologics License Application (BLA) – An application submitted when an applicant wishes to obtain marketing approval for a biological product.

Humanitarian Device Exemption (HDE) – An application that is similar to a premarket application (PMA), but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

Investigational Device Exemption (IDE) – An IDE allows an investigational device to be used in a clinical study.

Investigational New Drug (IND) – An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal tests results, and manufacturing information. It serves as a request for an exemption from the Federal statute that prohibits an unapproved drug or biological product from being shipped in interstate commerce.

New Drug Application (NDA) – The application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA.

Premarket Approval Application (PMA) – An application containing sufficient valid scientific evidence to ensure that a class III medical device is safe and effective for its intended use.

Premarket Notification [Traditional 510(k)] – A submission to demonstrate that a device to be marketed is as safe and effective, that is, substantially equivalent (SE), to a legally marketed device that is not subject to premarket approval. Applicants must compare their 510(k) device to one or more similar devices currently on the U.S. market and make and support their substantial equivalency claims.

> **Abbreviated 510(k) –** A method for demonstrating substantial equivalence that relies on the use of guidance documents, special controls and/or recognized standards to facilitate the 510(k) review.
>
> **Special 510(k)** – A method for demonstrating substantial equivalence that utilizes the design control requirement of the Quality System Regulation and may be submitted for a modification to a device that has been cleared under the 510(k) process. The Special 510(k) allows the manufacturer to declare conformance to design controls without providing the data.

This report was prepared by FDA's Office of Combination Products in collaboration with the Office of Planning, Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health. For information on obtaining additional copies contact:

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